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(21) International Application Number: PCT/GB98/03511 (22) International Filing Date: 25 November 1998 (25.11.98) (30) Priority Data: 9724786.0 25 November 1997 (25.11.97) GB (71) Applicant (for all designated States except US): DANBIOSYST UK LIMITED [GB/GB]; Albert Einstein Centre, Highfields Science Park, Nottingham NG7 2TN (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): WATTS, Peter [GB/GB]; Flat 2, 47 Highfield Road, West Bridgford, Nottingham NG2 6DR (GB). (74) Agent: BASSETT, Richard; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: MUCOSAL DELIVERY SYSTEM COMPRISING LIPOPHILIC THROMBIN INHIBITORS (57) Abstract <p>A composition for the delivery across a mucosal surface of a lipophilic thrombin inhibitor comprising a lipophilic thrombin inhibitor and a non-ionic surfactant. Preferably, the mucosal surface is in the gastrointestinal tract, nose, mouth, rectum or vagina. Advantageously, the thrombin inhibitor is a peptide boronic acid or ester derivative thereof. Conveniently, the non-ionic surfactant is an ethoxylated glyceride. Suitably, the composition is contained within a capsule. In addition, the invention also relates to methods of making said compositions and the use of said compositions in medicine.</p>		

MUCOSAL DELIVERY SYSTEM COMPRISING LIPOPHILIC THROMBIN INHIBITORS

Field of invention

The present invention relates to a means of delivering lipophilic thrombin
5 inhibitors across a mucosal surface, for example in the gastrointestinal tract, therein providing enhanced absorption of such drugs with corresponding systemic levels of drug.

Background

- 10 In the treatment of cardiovascular disorders, such as venous thrombosis, atrial fibrillation, arterial thrombosis, myocardial infarction and stroke, it can be advantageous to modify blood coagulation mechanisms in order to decrease the likelihood of clot formation.
- 15 An essential step in the blood clotting, or coagulation, cascade is the proteolytic cleavage of fibrinogen to release fibrinopeptides A and B. These peptides, in turn, lead to the generation of fibrin which can undergo polymerisation to form a haemostatic plug, or 'blood clot'. Although the blood coagulation cascade may be modulated at numerous different sites, a
20 rate limiting step in this process is the cleavage of fibrinogen, which is catalysed by the trypsin-like serine protease thrombin. Pharmacological agents which inhibit thrombin activity and thereby prevent the action of thrombin in the blood coagulation cascade have been studied in detail. Such anticoagulants drugs are termed thrombin inhibitors, and can be
25 grouped into three classes of compound; heparins, coumarins and low-molecular weight heparins. Of these, only the coumarins, *e.g.* warfarin, exhibit significant activity when administered orally.

All three classes of anticoagulant therapy act indirectly to inhibit
30 thrombin; heparin and low-molecular weight heparin by activation of

endogenous plasma proteins which inhibit thrombin and other proteases of the blood coagulation cascade, and coumarins by inhibition of the hepatic synthesis of vitamin K-dependent proteins (including thrombin). It is as a consequence of these indirect mechanisms that many of the limitations of these agents as therapeutics arise, in particular the need for careful dose titration in order to optimise therapeutic efficacy while minimising any side effects. Such complications include thrombocytopenia, autoimmune reactions and, in the case of warfarin, skin necrosis. However, arguably the most common problem with current thrombin inhibitor therapies is the occurrence of haemorrhagic complications, which can on occasion prove fatal.

Direct-acting thrombin inhibitors have been developed, notably hirudin, hirolog and argatroban, which have shown promise in clinical trials. However, like heparin and low-molecular weight heparin, they are also limited to parenteral administration routes due to their poor oral absorption properties. Recently, modern X-ray crystallographic techniques have facilitated the development of a further type of direct-acting thrombin inhibitor, termed reaction intermediate-based thrombin inhibitors, which interact with the catalytic site of the thrombin molecule. One class of such agents is the peptide-like structures containing boron, e.g. peptide-boronic acids and their ester derivatives (Tapparelli *et al.* 1993 *Trends in Pharmacological Sciences* 14, 366-376). These peptidomimetic drugs exhibit good antithrombotic activity when administered by injection but, owing largely to their peptidic nature, are poorly absorbed into the blood when given orally.

Current formulations for the oral delivery of a thrombin inhibitor across mucous membranes of the gastrointestinal tract are limited to those comprising coumarins, of which warfarin is the most efficacious and

consequently the most widely used example. Development of alternative orally active thrombin inhibitors has been hindered by limitations in the oral bioavailability, plasma half-life, safety and efficacy of other candidate thrombin inhibitors. This is especially true of the large number of small
5 molecular weight direct thrombin inhibitors that have been prepared and studied.

Hence, there is a need for further thrombin inhibitors which can be delivered across a mucosal surface.

10

The present invention seeks to provide a means of delivering lipophilic thrombin inhibitors across a mucosal surface.

Statement of invention

15 One aspect of the invention provides a composition for the delivery across a mucosal surface of a lipophilic thrombin inhibitor. Said composition comprises a lipophilic thrombin inhibitor and a non-ionic surfactant.

By 'thrombin inhibitor' we mean a compound which is able to
20 substantially inhibit, via direct or indirect means or both, the catalytic action of thrombin. Suitable tests for thrombin inhibitor activity of a compound include the activated partial thromboplastin time (APTT) test (Thomson JL and Poller L. The activated partial thromboplastin time. In: *Blood coagulation and haemostasis*. Ed. Thomson JM, Churchill
25 Livingstone, Edinburgh, 1989, pp301-339).

By 'lipophilic' we mean a compound having a partition coefficient between 1-n-octanol and water expressed as log P of greater than 1.0 at physiological pH and 25°C.

Advantageously, the mucosal surface is in the gastrointestinal tract, nose, mouth, rectum or vagina.

- 5 Preferably, the thrombin inhibitor is a direct-acting thrombin inhibitor. By 'direct-acting' we mean a thrombin inhibitor which inhibits the blood coagulation cascade by interacting directly with thrombin to inhibit fibrinogen cleavage.
- 10 Advantageously, the thrombin inhibitor is a peptide boronic acid or ester derivative thereof. For example, peptidomimetic thrombin inhibitors that would be suitable for formulation in the present invention include DUP 714 (acetyl(D)Phe-Pro-boroArg), SDZ 216744 benzyloxy-carboxyl-(D)-Phe-Pro-boromethoxypropylglycine-pinannediol, SDZ 217766 tert-but-
- 15 oxy-carbonyl-(D)-trimethylsilylalanine-Pro-boroArgpinannediol, SDZ 19349 tert-butoxycarbonyl-(D)-trimethyl-silylalanine-Pro-boromethoxy-propyl-glycine-pinannediol (Kettner *et al.*, 1990, *J. Biol. Chem.*, 265(30), 18289-97; EP 741747; EP 688336).
- 20 The thrombin inhibitor can be a prodrug. By 'prodrug' we mean an inactive compound which, when administered, undergoes conversion *in vivo* to an enzymically-active thrombin inhibitor. For example, Z-D-Phe-pro-borompg-Opinacol (formula weight $C_{33}H_{46}O_7N_3B$) (molecular weight 607.6) is a lipophilic prodrug of a thrombin inhibitor. Its synthesis has
- 25 been described in US 5,596,123. It will be referred to subsequently as TRI 50b. The molecule is essentially insoluble in water but has some solubility in oily vehicles. Prototype formulations for parenteral administration have been developed based on alcoholic vehicles with added excipients such as polyethylene glycol. However, while such
- 30 systems can have use in early animal and even human studies, they cannot

be considered as products for use in patients in the market place due to poor stability and possible toxic reactions to the chosen formulation additives.

- 5 Non-ionic surfactants are known in the art and are widely used as pharmaceutical excipients. By 'non-ionic' we mean a surfactant which is substantially free of ionic, *i.e.* electrically-charged, groups in the polar portion of the molecule. Such surfactants are normally non-toxic and non-irritant. Suitable non-ionic surfactants of the present invention include,
10 but are not limited to, alkyl ethers, castor oils, sorbitan fatty acid esters, stearates and glycerides (Wade and Weller, Handbook of Pharmaceutical Excipients 2nd edition, The Pharmaceutical Press, London).

Preferably, the non-ionic surfactant is ethoxylated. By 'ethoxylated' we
15 mean a surfactant containing one or more polyethylene glycol (PEG) groups. 'Ethoxylated' and 'polyglycolized' will be used interchangeably throughout this description. Conveniently, the surfactant contains between 4 and 20 ethoxyl (PEG) groups, for example between 10 and 16 ethoxyl groups. Suitably, the surfactant is a liquid, semi-solid or solid.

20

Ethoxylated surfactants suitable for use in this invention are known to those skilled in the art and include, but are not limited to, polyglycolized glycerides such as Gelucire® (produced by Gattefossé, Saint Priest, France). Polyglycolized glycerides are defined as compounds obtained by
25 polyglycolysis of natural hydrogenated oils with polyethylene glycols. The Gelucire® materials are a range of fatty excipients with different melting points and lipophilicities which are suitable for filling into gelatin capsules for oral administration. Gelucire® 37/06, a saturated polyglycolized glyceride with an oral LD 50 in the rat of greater than

50 ml/kg (Ash and Ash, 1995), is a preferred material for the present invention.

The content of the ethoxylated surfactant in the composition of the present invention can be from 5 to 90%, more preferably from 20 to 80% and, most preferably, from 40 to 70%. The composition may additionally contain a dispersing agent such as polysorbate 80 (Tween 80) in the amount of 1 to 50% most preferable from 5 to 20% and most preferably from 7 to 15%. Suitable dispersing agents are well-known in the art and include, but are not limited to, surfactants, silica and microcrystalline cellulose.

A preferred embodiment of the first aspect of the present invention are compositions comprising a lipophilic thrombin inhibitor and a non-ionic surfactant contained within a capsule suitable for mucosal administration. Such capsules are known to persons skilled in the art and include hard and soft capsules made from gelatin, starch or HPMC. Conveniently, the capsule has an enteric coating which enables it to stay intact within the stomach, allowing subsequent release of the thrombin inhibitor in the intestines.

A second aspect of the present invention provides a method of making a composition for the delivery across a mucosal surface of a lipophilic thrombin inhibitor, said means comprising admixing a lipophilic thrombin inhibitor with a non-ionic surfactant. The composition may be produced by co-melting and mixing together the drug and excipients at a temperature exceeding the melting point of the drug. Alternatively, the drug is dispersed in the melted surfactant; Gelucire® 37/06, for example, melts at 37°C. In a preferred embodiment, the mixture may then be filled

into capsules where it will cool to form a liquid or semi-solid at room temperature.

5 A further aspect of the present invention provides a composition for the delivery across a mucosal surface of a lipophilic thrombin inhibitor for use in medicine. For example, inhibitors of thrombin have utility in the treatment of venous thrombosis, atrial fibrillation, arterial thrombosis, pulmonary embolism, and in the prevention and treatment of cardiovascular disorders including myocardial infarction and stroke. The
10 clinical management of such disorders often necessitates a prolonged period of treatment with a thrombin inhibitor. In these circumstances, it is convenient and preferable to use an oral administration route.

Recently, novel applications of thrombin inhibitors in non-thrombotic
15 indications have been highlighted. For example, patients with cancer, neurodegenerative disease and certain inflammatory diseases, such as sepsis, commonly exhibit enhanced activity of the blood coagulation cascade, providing a rationale for symptomological treatment with thrombin inhibitors. However, there is evidence to suggest that thrombin
20 may be *directly* involved in the cellular pathophysiology of these diseases, *i.e.* thrombin activation may be causative rather than consequential. Thus, thrombin inhibitors may also have utility in the treatment of such diseases *per se* and not mere alleviation of their symptoms.

25 Preferred embodiments of the invention will now be described by way of example, with reference to the accompanying figures.

Examples

The thrombin inhibitor TRI 50b, a peptide boronic acid derivative (supplied by the Thrombosis Research Institute, London) was formulated
5 into three different oral delivery systems:

1. a simple semi-solid formulation based on polyethylene glycol and a polysorbate surfactant;
- 10 2. an homogenous liquid formulation based on an ethoxylated castor oil surfactant;
3. an homogeneous semi-solid formulation based on a ethoxylated glyceride surfactant with an additional dispersing agent.

All formulations were filled into hard gelatin capsules. In all
15 formulations, the amount of each constituent is given as a percentage by weight of the total weight of the composition (excluding the capsule weight).

An HPLC method was used to measure the content of TRI 50b in the
20 capsules. The chromatographic method resolved the two isomers of the drug. The combined peak area of the two components was used to calculate the content of the drug in the formulated products.

Formulation 1

25 This comprised a solution of the following:

◦ TRI 50b	33.3% w/w
◦ PEG 400	56.7% w/w
◦ Tween 80	10.0% w/w

PEG 400 (polyethylene glycol 400, Sigma, Poole, UK) is a widely used pharmaceutical excipient listed in British, European and US pharmacopoeias. It is essentially non-toxic and non-irritant (Wade and
5 Weller, 1994). It is approved by the FDA for defined uses (Ash and Ash, 1995).

Tween 80 (Polysorbate 80, Sigma, Poole, UK) is a widely used pharmaceutical excipient listed in British, European and US
10 Pharmacopoeias. It is essentially non-toxic and non-irritant (Wade and Weller, 1994). This material is UK approved and FDA approved for the following uses: buccal, intramuscular injectable, intravenous, parenteral, ophthalmic, oral, otic, rectal, topical and vaginal. This material is a surfactant added to increase the dispersion of the drug in the mixture.

15

The TRI 50b content of the hard gelatin capsules was checked by HPLC. The results showed a concentration of 300 mg/ml (theoretical value 333 mg/ml).

20 *Formulation 2*

This comprised an homogeneous liquid of the following:

- TRI 50b 33.3% w/w
- Cremophor EL® 66.7% w/w

25

Cremophor EL® (polyoxyethylene 35 castor oil, BASF, Cheadle, UK) is a water soluble material which is widely used as a pharmaceutical excipient in oral, topical and parenteral formulations. It is essentially non-toxic and non-irritant. This material is listed in USP NF XVII (Wade and Weller,
30 1994).

The TRI 50b content of the hard gelatin capsules was checked by HPLC. The results showed a concentration of 292 mg/ml (theoretical value 333 mg/ml). Cremophor EL® gave rise to interfering peaks and the
5 HPLC conditions used were adjusted to prevent this interference.

Formulation 3

This comprised an homogeneous semi-solid:

10	◦ TRI 50b	33.3% w/w
	◦ Gelucire® 37/06	56.7% w/w
	◦ Tween 80	10.0% w/w

Gelucire® 37/06 is a saturated polyglycolized glyceride (Gattefossé, Saint
15 Priest, France). The Gelucire® materials are a range of fatty excipients with different melting points and lipophilicities which are suitable for filling into gelatin capsules for oral administration. Gelucire® 37/06 melts at 37°C and forms a dispersion in water. The oral LD50 in the rat is greater than 50 ml/kg. (Ash and Ash, 1995).

20

The TRI 50b content of the hard gelatin capsules was checked by HPLC. The results showed a concentration of 306 mg/ml (theoretical value 333 mg/ml).

25 Evaluation of formulations in a pig model

The three formulations were evaluated in the mini pig by pharmacokinetic testing. The animals were dosed directly into the duodenum, blood samples were collected at various time-points and the samples analysed for TRI 50b content (using an HPLC method) and thrombin clotting times by
30 the Thrombosis Research Institute, London.

TRI 50b plasma levels

Figure 1 shows the effect of three different formulation compositions (formulation 1 - ○, formulation 2 - △, formulation 3 - □) on plasma concentration of TRI 50b following administration of 20 mg/kg TRI 50b to the mini pig. Animals were dosed directly into the duodenum at time = 0 minutes, and blood samples were collected and analysed for drug content using HPLC.

Thrombin clotting times

Figure 2 shows the effect of three different formulation compositions (formulation 1 - ○, formulation 2 - △, formulation 3 - □) on thrombin clotting time. Animals were dosed directly into the duodenum at time = 0 minutes, and blood samples were collected and analysed. Clotting time was assessed at a temperature of 37°C and a pH of 7.4 in the presence of calcium ions.

It is apparent that thrombin times tended to mirror the plasma concentrations of compound.

20

Bioavailability is the fraction or percentage of a dose that reaches the systemic circulation intact, as compared to an intravenous injection. When administered at a doses of 20 mg/kg, TRI 50b was found to have bioavailabilities of 10.3%, 13.2% and 41.0% from formulations 1, 2 and 3, respectively, calculated as the AUC (area under the curve) for the oral formulation as a percentage of the AUC following direct injection.

25

Thus, formulation 3, which contained the saturated polyglycolized glyceride (Gelucire®), was found to produce a dramatic and surprising

increase in the measured bioavailability of the lipophilic thrombin inhibitor TRI 50b.

References

- 5
1. Ash and Ash (Eds.) (1995) *Handbook of Pharmaceutical Additives*, Gower Publishing Ltd, London.
 2. Kettner *et al.* (1990) *J. Biol. Chem.*, 265(30), 18289-97
 3. Tapparelli C *et al.* (1993) *Trends in Pharmacological Sciences* 14,
10 366-376
 4. Thomson JM and Poller L (1989) The activated partial thromboplastin time. In: *Blood coagulation and haemostasis*. Ed. Thomson JM, Churchill Livingstone, Edinburgh, pp301-339.
 5. Wade A and Weller PJ (1994) *Handbook of Pharmaceutical Excipients*
15 2nd edition, The Pharmaceutical Press, London.

Claims:

1. A composition for the delivery across a mucosal surface of a lipophilic thrombin inhibitor comprising a lipophilic thrombin inhibitor
5 and a non-ionic surfactant.
2. A composition of claim 1 wherein the mucosal surface is in the gastrointestinal tract, nose, mouth, rectum or vagina.
- 10 3. A composition of claim 1 wherein the lipophilic thrombin inhibitor is a direct-acting thrombin inhibitor.
4. A composition of claim 1 wherein the thrombin inhibitor is a peptide boronic acid or ester derivative thereof.
- 15 5. A composition of claim 1 wherein the thrombin inhibitor is an inactive prodrug capable of undergoing a conversion to produce an active thrombin inhibitor.
- 20 6. A composition of claim 1 wherein the surfactant is an alkyl ether, castor oil, sorbitan fatty acid ester, stearate or glyceride.
7. A composition of claim 6 wherein the surfactant is ethoxylated.
- 25 8. A composition of claim 7 wherein the surfactant has between 4 and 20 ethoxyl groups attached, for example between 10 and 16 ethoxyl groups.
9. A composition of claim 7 or 8 wherein the surfactant is a glyceride.

10. A composition of claim 9 wherein the glyceride is saturated.
11. A composition of claim 9 wherein the glyceride is at a
5 concentration of between 5 and 90% (w/w), for example between 20 and 80%, or between 40 and 70%.
12. A composition of claim 1 which additionally contains a dispersing agent.
10
13. A composition of claim 12 wherein the dispersing agent is a surfactant, silica or microcrystalline cellulose.
14. A composition of claim 12 wherein the dispersing agent is at a
15 concentration of between 1 and 50% of the total composition (w/w), for example between 5 and 20%; or between 7 and 15%.
15. A capsule suitable for mucosal administration containing a composition of any one of claims 1 to 14.
20
16. A capsule of claim 15 wherein the capsule comprises gelatin, starch or HPMC.
17. A method of making a composition of any one of claims 1 to 14
25 comprising admixing a lipophilic thrombin inhibitor and a non-ionic surfactant.
18. A method of claim 17 further comprising admixing a dispersing agent.

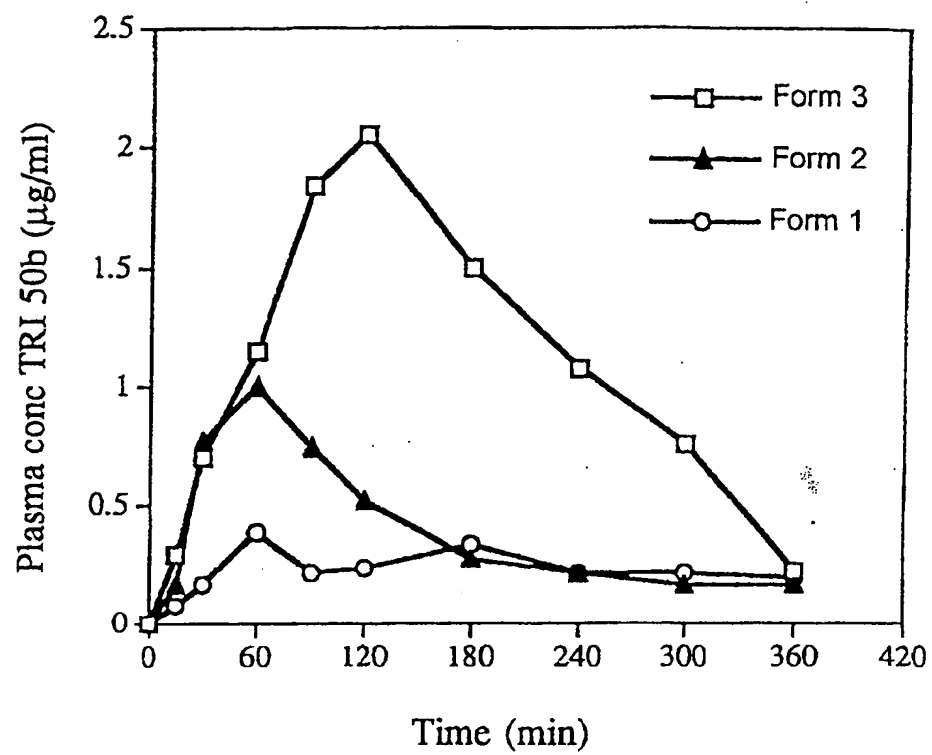
19. A method of claim 17 or 18 further comprising containing said mixture in a capsule suitable for mucosal administration.

5 20. A composition of any one of claims 1 to 14 for use in medicine.

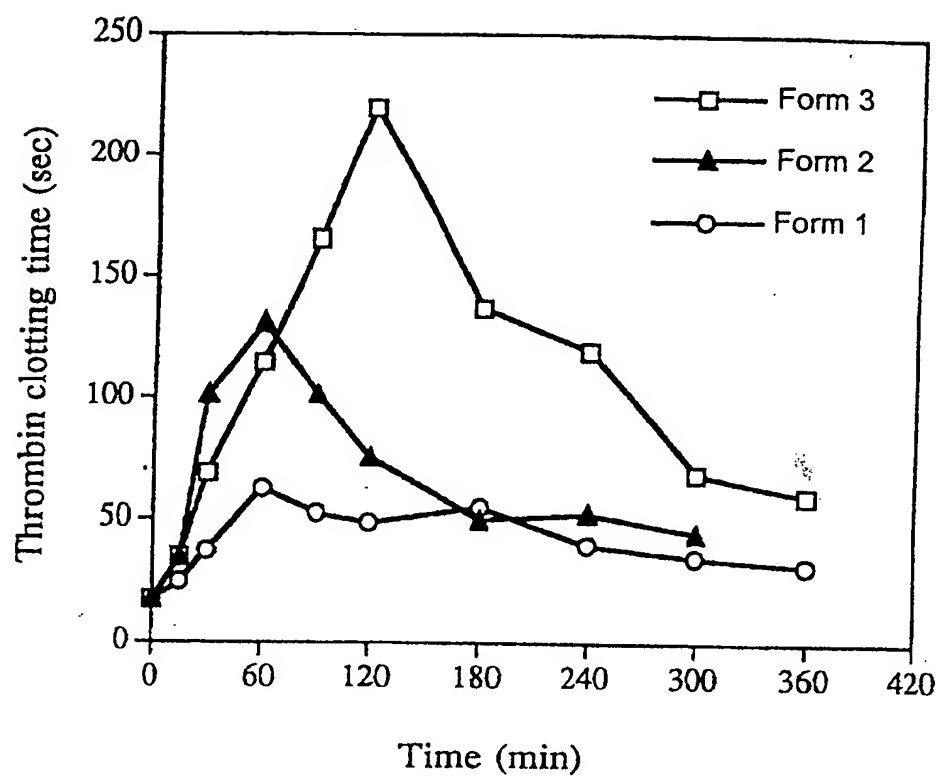
21. Use of a composition of any one of claims 1 to 14 in the preparation of a medicament for the delivery of a lipophilic thrombin inhibitor across a mucosal surface.

10

22. Use according to claim 21 in the preparation of a medicament for treatment of cardiovascular disorders.

1/2*Figure 1*

2/2

*Figure 2*

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/03511

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0391369 A	10-10-1990	IL 93558 A	27-11-1995
		AT 110563 T	15-09-1994
		AU 614465 B	29-08-1991
		AU 5292790 A	11-10-1990
		CA 2013755 A,C	05-10-1990
		DE 69011922 D	06-10-1994
		DE 69011922 T	12-01-1995
		JP 2083211 C	23-08-1996
		JP 2290809 A	30-11-1990
		JP 7121857 B	25-12-1995
		US 5364632 A	15-11-1994
WO 9420526 A	15-09-1994	AT 153670 T	15-06-1997
		AU 677297 B	17-04-1997
		AU 6208094 A	26-09-1994
		CA 2153656 A	15-09-1994
		DE 69403459 D	03-07-1997
		DE 69403459 T	02-01-1998
		DK 688336 T	20-10-1997
		EP 0688336 A	27-12-1995
		ES 2101516 T	01-07-1997
		GR 3023577 T	29-08-1997
		HU 72735 A	28-05-1996
		JP 8507501 T	13-08-1996
		NZ 262415 A	28-10-1996
		PL 310940 A	08-01-1996
		SG 52766 A	28-09-1998
		ZA 9401501 A	04-09-1995

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/03511

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/55 A61K31/69 A61K47/14 A61K47/06 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 391 369 A (YISSUM RES DEV CO) 10 October 1990 see page 4, line 9-13; claim 1	1-22
Y	KETTNER C ET AL: "THE SELECTIVE INHIBITION OF THROMBIN BY PEPTIDES OF BOROARGININE" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 30, 25 October 1990, pages 18289-18297, XP000160262 cited in the application see abstract	1-22
Y	WO 94 20526 A (SANDOZ AG ;SANDOZ AG (DE); SANDOZ LTD (CH); COOK NIGEL SCOTT (CH);) 15 September 1994 cited in the application see claim 15	1-22

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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